Testing menstrual blood for human papillomavirus during cervical cancer screening in China: cross sectional population based study

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ABSTRACT

OBJECTIVE

To compare the diagnostic accuracy of minipad collected menstrual blood versus clinician collected cervical samples to test for human papillomavirus (HPV) in the detection of cervical intraepithelial neoplasia grade 2/3 or worse (CIN2+/CIN3+).

DESIGN

Cross sectional population based study.

SETTING

Four urban and three rural communities in Hubei Province, China.

PARTICIPANTS

3068 women aged 20-54 years with regular menstrual cycles, enrolled between September 2021 and January 2025.

INTERVENTIONS

HPV testing using minipad collected menstrual blood, clinician collected cervical samples, and ThinPrep cytology. Women who tested HPV positive by either collection method or by cytology (atypical squamous cells of undetermined significance or worse) were referred for colposcopy directed biopsy sampling.

MAIN OUTCOME MEASURE

Diagnostic accuracy for detecting CIN2+ and CIN3+.

RESULTS

Among 3068 participants, minipad based HPV testing showed a sensitivity of 94.7% (95% confidence interval 80.9% to 99.1%) for CIN2+ detection, comparable to clinician based HPV testing (92.1%, 77.5% to 97.9%; P=1.00). Although minipad HPV testing showed a lower specificity than clinician HPV testing (89.1%, 88.0% to 90.2% *v* 90.0%, 88.9% to 91.1%; P=0.001), the negative predictive value matched that of clinician HPV testing (99.9%, 99.7% to 100.0% *v* 99.9%, 99.7% to 100.0%; P=1.00). Both collection methods had a similar positive predictive value (9.9%, 7.1% to 13.5% *v* 10.4%, 7.4% to 14.3%; P=0.82) and screening efficiency (10.1 *v* 9.6 referrals per CIN2+ detected; P=0.82).

CONCLUSIONS

Minipad collected menstrual blood showed comparable diagnostic accuracy to clinician collected cervical samples for HPV testing for detecting CIN2+ and CIN3+.

TRIAL REGISTRATION

ClinicalTrials.gov NCT06082765.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Testing menstrual blood for human papillomavirus (HPV) shows promise as a non-invasive alternative to cervical cancer screening, with pilot studies reporting high concordance of HPV genotypes with clinician collected cervical samples

Evidence is, however, limited by small hospital based cohorts, non-standardised collection devices, and lack of real world validation for detecting high grade cervical intraepithelial neoplasia grade 2/3 or worse

WHAT THIS STUDY ADDS

The results of this large scale community based study show the utility of using minipad collected menstrual blood for HPV testing as a standardised, non-invasive alternative or replacement for cervical cancer screening

Integration with the Early Test mobile app further streamlined result reporting and patient communication, enhancing the feasibility of large scale implementation of screening

The findings of this study support the integration of menstrual blood based HPV testing into national cervical cancer screening guidelines

Introduction

Persistent infection with high risk human papillomavirus (HPV) is a key factor in the oncogenesis of cervical cancer,[1 2] resulting in about 348 000 deaths annually.[3] Despite being largely preventable, cervical cancer is newly diagnosed in around 661 000 women each year, with 85% of diagnoses occurring in developing countries.[3] At present, HPV testing is the principal approach for cervical cancer screening,[4] reducing the incidence and mortality rates of cervical cancer.[5 6] However, various factors, including insufficient medical infrastructure, lack of health awareness, religious and cultural inequities, and fear of pain can affect women's acceptance of clinician sampling, hindering effective implementation of screening.[7 8] To deal with these challenges, several self-sampling methods have been developed as alternatives to the clinician collected approach, including vaginal swabs,[9] cervicovaginal brushes,[10] and tampons.[11] These methods have achieved relative sensitivities ranging from 77% to 96% and relative specificities ranging from 90% to 101% for detecting cervical intraepithelial neoplasia grade 2 or worse (CIN2+, see supplementary appendix table S1).[9 10 12-20] However, barriers to adoption persist, including discomfort from the procedure,[21] cultural

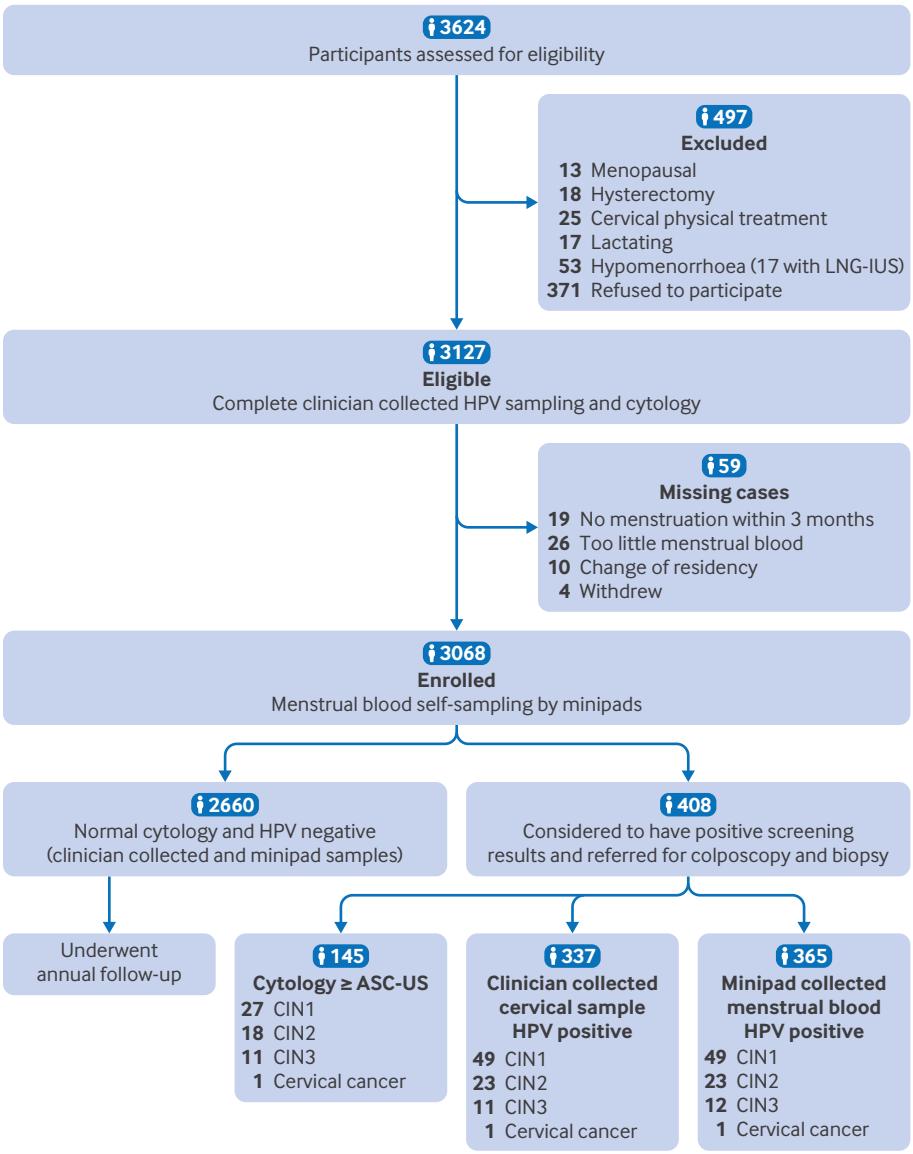

Fig 1 | Study flow diagram and procedures. ≥ASC-US=atypical squamous cells of undetermined significance or higher grade; CIN=cervical intraepithelial neoplasia; HPV=human papillomavirus; LNG-IUS=levonorgestrel intrauterine system

concerns about vaginal manipulation,[22] and technical difficulties with sample collection.[23]

Distinct from other self-sampling methods, menstrual blood collection using sanitary pads represents a promising innovation, offering a convenient and non-invasive alternative that synchronises with women's natural menstrual cycles.[24] A prospective observational study reported that HPV results from menstrual blood samples aligned more closely with clinician collected cervical samples than with vaginal swab samples.[21] Notably, 92% of participants preferred self-collection over clinician collection, with 94% favouring a modified menstrual pad containing a paper based dried blood spot strip (Q-Pad) over vaginal swabs, and 22.9% opted out due to discomfort with vaginal swabs. Our cross sectional pilot study using next generation sequencing technology on 120 participants also showed high concordance (κ=0.763) with clinician sampling for HPV detection.[25]

However, whether testing menstrual blood for HPV can be implemented as a useful cervical cancer screening tool in large scale community population remained unanswered. A 2022 systematic review[24] highlighted the potential of menstrual blood HPV testing but summarised that previous studies were constrained by small samples sizes[21 25-30]; hospital based settings not reflecting community populations[25 26 28 29]; lack of a standardised collection device[30] to ensure standardisation and reproducibility; and absence of the diagnostic accuracy of menstrual blood versus clinician HPV testing for detection of cervical lesions in real world settings.[21 25-29]

To address the evidence gap about the accuracy of using menstrual blood to test for HPV in large populations and to assess its potential as a replacement[31] for clinician HPV testing, we conducted a large scale cross sectional cervical cancer screening study. This study evaluated the diagnostic accuracy

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of minipad collected menstrual blood for HPV testing compared with clinician collected cervical samples for HPV testing for detecting cervical intraepithelial neoplasia grade 2/3 or worse (CIN2+/CIN3+) in a community based population.

Methods

Participants and procedures

Setting

From September 2021 to January 2025, we conducted a community based, prospective study in seven sites in Hubei Province, China (fig 1 and supplementary appendix file S1). The sites included four urban communities (Fruit Lake Community of Wuhan City, Jiang'an District of Wuhan City, Huangzhou district of Huanggang County, and Jingling Community of Tianmen County) and three rural communities (Liutang Community of Huangmei County, Gongtang Community of Zhongxiang City, and Chaihu Community of Zhongxiang City).

Eligibility

Women were assessed for eligibility with prespecified criteria. Inclusion criteria were regular menstrual cycles (21-35 days),[32] previous sexual activity, presence of a cervix, and signed informed consent. Exclusion criteria were hypomenorrhoea (menstrual blood volume <5 mL per cycle),[33] pregnancy or lactation, menopause or history of hysterectomy, history of cervical physical treatment (cryotherapy or laser therapy), and acute or subacute infections of the reproductive system.

Identification and enrolment

Trained community healthcare workers used official community residential population registries to consecutively identify women aged 20-60 years, and directly contacted those who met the criteria. Potential participants were contacted by phone, provided with study information in their local dialect when needed (professional interpreters available), and invited to attend the community healthcare centre. Women who consented were enrolled.

Specimen collection

Each participant provided three separate specimens: a minipad collected menstrual blood specimen for HPV testing (index test), a clinician collected cervical specimen for HPV testing (comparator test), and a clinician collected cervical specimen for ThinPrep cytology. Eligible participants received minipads along with written instructions and were asked to collect a menstrual blood specimen within three months and return the pad either directly to community healthcare workers (who mailed it to the central laboratory) or by post.

Verification pathway and follow-up

Participants with any positive result (HPV positive on either specimen or cytology showing atypical squamous cells of undetermined significance or higher grade) were referred for colposcopy directed biopsy. Participants with dual negative results (HPV negative on both tests and normal cytology) were not referred for biopsy and were scheduled for annual follow-up in the community. This study followed the current standard clinical pathway in line with international guidelines.[34-38] Women with dual negative screening results were not referred for colposcopy directed biopsy because their 3-5 year risk of CIN2+ is extremely low (around 0.1%).[39-42] Biopsies in this group would be clinically unwarranted and expose patients to invasive procedures with potential harms (eg, pain, bleeding, and infection).[43]

Cytology and clinician HPV testing

Specialised gynaecologists collected cervical samples for cytology and HPV testing. After the participant had emptied her bladder, the cervix was visualised using a speculum. Cervical exfoliated cells were collected using a cytology brush and stored in the tubes with cell preservation solution (GeneRulor, China) for liquid based cytology. An experienced pathologist interpreted the cytology results. According to the Bethesda classification system,[44] the results were categorised as negative for intraepithelial lesion or malignancy, atypical squamous cells of undetermined significance, atypical squamous cells cannot exclude high grade squamous intraepithelial lesion, low grade squamous intraepithelial lesion, high grade squamous intraepithelial lesion, atypical glandular cells, and invasive cancer.

Genotyping of HPV DNA for clinician collected samples was performed with the HPV GenoArray diagnostic kit (Hybribio Biotech, China), which is approved by the National Medical Products Administration of China and has been applied in multiple cervical screening studies.[45 46] The assay genotypes 14 HPV types (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) designated by the World Health Organization.[34] According to the manufacturer's instructions, samples containing ≥500 copies/μL are classified as HPV positive and those below this threshold are classified as HPV negative.[47]

Menstrual blood collection and HPV testing

Device

We developed a research-only prototype sampling strip for collecting menstrual blood (10.0×2.0×0.2 cm) composed of presterilised cotton optimised for DNA preservation and recovery (fig 2). This minipad adheres easily to the absorbent area of a standard sanitary pad, enabling women to use their preferred commercial sanitary product while ensuring standardised specimen collection. The device is not commercially available.

Participant instructions and collection

Each participant received a minipad, a sterile container prefilled with cell preservation solution, and detailed instructions. Participants attached the minipad to the middle anterior absorbent surface of the sanitary

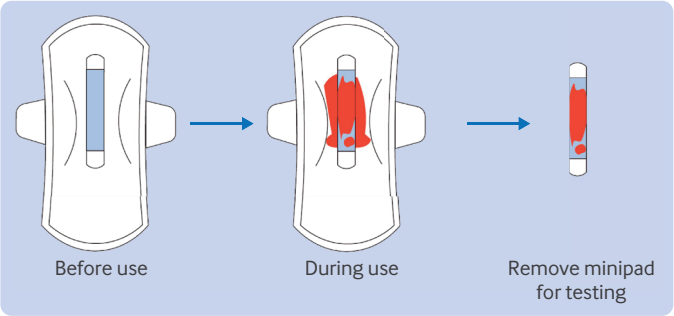

Fig 2 | Minipad product and usage

pad at the start of the menstrual cycle. When more than two thirds of the minipad surface were visibly saturated with menstrual blood, participants removed the strip, placed it in the preservation solution, sealed the container, and returned the sample to the central laboratory.

Laboratory processing

On receipt, specimens were stored at 4°C pending processing. DNA was then extracted according to a prespecified protocol and stored at −20°C until analysis. Supplementary appendix file S2 provides detailed standard operating procedures for handling the minipad, extracting DNA, and testing for HPV.

Participant results platform

To facilitate timely return of results, we provided an optional WeChat mini-program mobile app entitled Early Test. Participants could register basic identifiers (name, ID number, age, phone number) by scanning a quick response code (supplementary appendix file S3). The platform offered immediate access to test results, with clear interpretation, secure messaging with healthcare providers, and educational resources on HPV and cervical health. Healthcare providers responded to inquiries and offered counselling through the platform.

Colposcopy directed biopsy

Colposcopy uses a special magnifying instrument that allows clinicians to closely examine the cervix. The procedure is performed when cervical screening detects a suspected abnormality that if left untreated could potentially develop into cervical cancer. Referral for colposcopy is recommended for women with HPV positive results from minipad collected menstrual blood or clinician collected samples, cytology showing atypical squamous cells of undetermined significance or higher grade,[48] and gross lesions suspicious of cancer.

Colposcopy directed biopsies, performed by experienced gynaecologists, provide histological diagnosis of abnormal changes to squamous cells in the cervix.[34] These changes are graded as mild (CIN1), moderate (CIN2), severe (CIN3), and cancer based on the depth of the abnormal cell layers.[4] CIN2+ denotes CIN2, CIN3, and cervical cancer, which typically require treatment.[49] The laboratory technicians, colposcopists, and pathologists were blinded to the results (minipad and clinician HPV testing and cytology).

Statistical analysis

Sample size calculation

Sample size was determined to assess concordance in detection of HPV genotype between minipad collected and clinician collected samples under a staged screening protocol, where HPV positive participants would undergo colposcopy directed biopsy. The calculation was based on an expected κ=0.8, assuming an HPV positivity rate of 10%. To ensure sufficient precision in assessing the agreement between the two sampling methods, we aimed for a two sided 95% confidence interval (CI) with a width of 0.05, setting the standard deviation of κ at 0.5. Using these parameters, the required sample size was calculated to be 1537. Considering a 20% dropout rate, the final adjusted minimal sample size was 1922 participants.[50] The substantial over-recruitment to 3068 participants resulted from high community response rates and continued recruitment until the predetermined study closure date.

Diagnostic accuracy analysis

CIN2+ and CIN3+ status were ascertained by histopathology among women referred for colposcopy directed biopsy (reference test). Women with dual negative screening results were classified as being true negative for disease, consistent with previous large scale studies[39-42] showing extremely low prevalence of CIN2+ in this group (eg, Shanxi Province Cervical Cancer Screening study: 1/1511, 0.07%[39]). Diagnostic accuracy estimates were calculated on this basis, a practice widely adopted in extensive clinical studies.[9 51-53]

The index test was minipad collected menstrual blood for HPV testing, with clinician collected HPV testing as the comparator. The reference test was histological diagnosis based on colposcopy directed biopsy. Women were considered to have true negative test results when intraepithelial lesion or malignancy and HPV were not detected using both collection methods, or when abnormality was detected during screening (HPV positive using either collection method, or cytology showing atypical squamous cells of undetermined significance or higher grade) but normal histological findings.

Absence of CIN2+ was defined as women with true negative test results and patients with CIN1. Absence of CIN3+ was defined as women with true negative test results and patients with CIN1 or CIN2.

For each test, we estimated sensitivity, specificity, positive predictive value, and negative predictive value from 2×2 contingency tables, with 95% CIs based on the Wilson score method.[54] Screening efficiency was determined as number of colposcopies required to diagnose CIN in one woman (number of women referred divided by number of CIN2+ or CIN3+ identified) and

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compared using the χ^2 test. Because sensitivity and specificity depend on disease status and provide paired outcomes for the same individuals, we used exact McNemar tests (two sided) to compare minipad versus clinician HPV testing. Positive and negative predictive values depend on the test result and therefore have different denominators across assays; we compared these using χ^2 tests for independent proportions.[20 53]

Non-inferiority assessment

We assessed non-inferiority of minipad versus clinician HPV testing using predefined margins for relative sensitivity (≥0.90) and relative specificity (≥0.98).[55] These thresholds align with international consensus criteria for the evaluation of new HPV detection assays.[56] A matched non-inferior statistic was used to test non-inferiority (supplementary appendix note 1).[57]

Corrected sensitivity and specificity analysis

To address potential bias from incomplete follow-up histological verification among screen negative participants, we performed a correction analysis. Using the incidence for CIN2+ observed in the Shanxi Province Cervical Cancer Screening study,[39] we estimated the number of missed diagnoses of CIN2+ among participants with dual negative screening results and calculated the corrected sensitivity and specificity using 2×2 contingency tables, with 95% CIs based on the Wilson score method (supplementary appendix note 2).[54]

Genotype concordance analysis

We assessed concordance in HPV genotypes detected by minipad collected versus clinician collected samples using the κ statistic.[58] Concordance was defined as[21 25 59]: complete concordance—identical HPV genotype profiles using both methods; partial concordance—at least one overlapping genotype but with additional non-overlapping genotypes using either method; and discordance—no overlap in HPV genotypes between methods. Overall concordance was measured as any overlap in HPV genotypes (complete+partial concordance). κ values ranging from 0.81 to 1.00 indicate almost perfect to perfect agreement.

All statistical analyses were performed using SPSS (V29.0). Unless otherwise specified, tests were two sided, with P<0.05 considered statistically significant.

Patient and public involvement

No participants or members of the public contributed to the study design, conduct, analysis, or recruitment as the study was initiated before patient and public involvement was common.

Results

Study population

Between September 2021 and January 2025, a total of 3624 individuals were assessed for eligibility. Overall, 497 women were excluded (refused to participate, n=371; menopausal, n=13; hysterectomy, n=18; cervical physical treatment, n=25; lactating, n=17; hypomenorrhoea, n=53, including 17 with levonorgestrel intrauterine system). Complete clinician collected HPV and cytology specimens were obtained from the 3127 enrolled participants. Of these, 59 individuals did not return a valid menstrual blood specimen (no menstruation within three months, n=19; too little menstrual blood, n=26; change of residence, n=10; withdrew, n=4). Finally, 3068 participants (aged 20-54 years) with complete results for all three screening tests (fig 1) were enrolled in the study. Initial HPV test failures occurred in 0.46% (14/3068) of clinician collected samples and 2.1% (64/3068) of cytology specimens due to insufficient sampling material; all were successfully repeated and provided valid results.

Participants were enrolled from seven sites in Hubei Province: 1723/3068 (56.2%) from urban communities and 1345/3068 (43.8%) from rural communities (table 1). Overall, 654 women were aged <30 years (21.3%), 1475 were aged 30-39 years (48.1%), and 939 were aged 40 years or older (30.6%). Educational level was middle school or lower in 378 participants (12.3%), high school in 1167 participants (38.0%), and college or higher in 1523 participants (49.6%). All participants were cisgender women of Han ethnicity and regular users of sanitary pads. They all had access to primary healthcare providers through our study sites.

Overall, 337 women tested positive for HPV by clinician sampling (11.0%) and 2731 tested negative (89.0%). Among HPV positive women, 107 were infected with HPV16/18 (3.5%, 107/3068) and 230 were infected with other HPV types (7.5%, 230/3068). Referral to colposcopy directed biopsy occurred in 408 women with any abnormal result (HPV positive on either specimen and/or cytology showing atypical squamous cells of undetermined significance or higher grade), 52 of whom had a diagnosis of CIN1, 24 a diagnosis of CIN2, 13 a diagnosis of CIN3, and one a diagnosis of invasive cervical cancer.

Diagnostic accuracy of minipad *v* clinician collected samples

Based on diagnostic accuracy analysis involving the 3068 participants, minipad collected samples showed comparable performance to clinician collected cervical samples for HPV testing and detecting high grade cervical lesions. For CIN2+ detection, minipad based HPV testing showed sensitivity similar to clinician sampling based HPV testing (94.7%, 95% CI 80.9% to 99.1% *v* 92.1%, 77.5% to 97.9%; P=1.00), and a higher point estimate than cytology (78.9%, 62.2% to 89.9%), although not statistically different (P=0.11; table 2 and supplementary appendix table S2). Specificity was lower for minipad based HPV testing (89.1%, 95% CI 88.0% to 90.2%) versus clinician sampling based HPV testing (90.0%, 88.9% to 91.1%; P=0.001), although both were substantially lower than for cytology (96.2%, 95.4% to 96.8%; P<0.001; table

Table 1 | Baseline characteristics. Values are number (percentage) unless stated otherwise

Characteristics	Total (n=3068)
Mean (SD) age (years)	35.7 (7.3)
Age groups (years):	
<30	654 (21.3)
30-39	1475 (48.1)
≥40	939 (30.6)
Community setting:	
Urban	1723 (56.2)
Rural	1345 (43.8)
Education:	
Middle school or lower	378 (12.3)
High school	1167 (38.0)
College or higher	1523 (49.6)
Clinician collected HPV testing:	
HPV negative	2731 (89.0)
HPV positive	337 (11.0)
HPV16/18	107 (3.5)
Other HPV types	230 (7.5)
Cytology:	
NILM	2923 (95.3)
≥ASC-US	145 (4.7)
ASC-US	103 (3.4)
ASC-H	7 (0.2)
LSIL	29 (0.9)
HSIL	6 (0.2)
AGC	0 (0.0)
Invasive cancer	0 (0.0)
Disease status:	
CIN1	52 (1.7)
CIN2	24 (0.8)
CIN3	13 (0.4)
Cervical cancer	1 (0.0)

AGC=atypical glandular cells; ASC-US=atypical squamous cells of undetermined significance; ≥ASC-US=atypical squamous cells of undetermined significance or higher grade; ASC-H=atypical squamous cells cannot exclude HSIL; CIN=cervical intraepithelial neoplasia; HPV=human papillomavirus; HSIL=high grade squamous intraepithelial lesion; LSIL=low grade squamous intraepithelial lesion; NILM=intraepithelial lesion or malignancy; SD=standard deviation.

2). No significant difference was observed in positive predictive value between minipad based HPV testing (9.9%, 95% CI 7.1% to 13.5%) and clinician sampling based HPV testing (10.4%, 95% CI 7.4% to 14.3%; P=0.82). The negative predictive value was identical for both collection methods (99.9%, 95% CI 99.7% to 100.0%; P=1.00; table 2). As to referral for colposcopy, the number of colposcopies needed to detect one woman with CIN2+ was comparable between minipad based and clinician sampling based HPV testing (10.1 *v* 9.6, P=0.82).

For CIN3+ detection, sensitivity was maintained when using minipad based HPV testing (92.9%, 95% CI 64.2% to 99.6%) similar to both comparator tests (clinician sampling based HPV testing 85.7%, 56.2% to 97.5%; cytology 85.7%, 56.2% to 97.5%; P=1.00; table 2). Specificity patterns were similar to those for CIN2+, with minipad based HPV testing (88.5%, 95% CI 87.3% to 89.6%) lower than clinician sampling based HPV testing (89.4%, 88.2% to 90.4%; P=0.001; table 2). Positive and negative predictive values did not differ significantly between the two collection methods (P=1.00; table 2). Colposcopy rates were identical for both methods (28.1 per diagnosis; P=1.00; table 2 and supplementary appendix table S3).

A non-inferiority test confirmed the comparable performance between minipad based HPV testing and clinician sampling based HPV testing (supplementary appendix table S4). Relative sensitivity was 1.03 (95% CI 0.91 to 1.16; P=0.01) for CIN2+, while relative specificity was 0.99 (0.97 to 1.01; P=0.001), meeting the non-inferior consensus criteria for HPV detection (relative sensitivity ≥0.90; specificity ≥0.98).

Genotype distribution: minipad *v* clinician HPV testing

Supplementary appendix figure S1 illustrates the distribution of HPV genotypes derived from minipad based HPV testing and clinician sampling based HPV testing. Among HPV positive participants in the minipad group, the most prevalent HPV genotypes were HPV52 (31.2%, 114/365), HPV16 (26.6%, 97/365), and HPV58 (25.2%, 92/365). Clinician HPV testing showed similar characteristics of predominant HPV genotypes, with HPV52 (33.5%, 113/337), HPV16 (24.3%, 82/337), and HPV58 (26.1%, 88/337) also being the most frequently detected genotypes (supplementary appendix figure S1A).

Because HPV16 and HPV18 are recognised as the two most oncogenic genotypes,[60] we analysed their prevalence separately. Minipad collected samples identified HPV16 or HPV18 in 37.5% (137/365) of women with positive results, with other HPV genotypes comprising 62.5% (228/365). In clinician collected samples, HPV16 or HPV18 were detected in 31.8% (107/337) of women with positive results, while other HPV genotypes accounted for 68.2% (230/337) (supplementary appendix figure S1B). Multiple HPV infections were observed in 46.8% (171/365) of minipad collected positive samples and 43.3% (146/337) of clinician collected positive samples (supplementary appendix fig S1C).

Age stratified analysis of minipad collected samples showed HPV detection rates of 18.3% (120/654) in women younger than 30 years, 10.7% in those aged 30-39 years, and 9.3% in women aged 40 years or older. Clinician collected samples showed detection rates of 18.2% (119/654) in women younger than 30 years, 9.8% in those aged 30-39 years, and 7.9% in those aged 40 years or older (supplementary appendix figure S1D).

Genotype concordance analysis

Analysis of genotype concordance between minipad based HPV testing and clinician based HPV testing showed complete concordance in 2951 participants (96.2%), partial concordance in 45 (1.5%), and discordance in 72 (2.3%). The overall genotype concordance rate was 97.7% (95% CI 97.0% to 98.1%), with a κ of 0.891 (0.866 to 0.916) (table 3).

Among the 365 participants with minipad based HPV positive results, complete genotype concordance was observed in 268 (73.4%), partial genotype concordance in 45 (12.3%), and genotype discordance in 52 (14.2%). Supplementary appendix table S5 lists the HPV genotype profiles of the 97 women.

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Table 2 | Diagnostic accuracies of cervical screening methods for detection of CIN2+ and CIN3+. Values are number/total number (percentage, 95% CI) unless stated otherwise

	Sample type for HPV testing				
	Minipad collected menstrual blood	Clinician collected cervical cells	Cytology ≥ASC-US	P value*	P value†
CIN2+					
Sensitivity	36/38 (94.7, 80.9 to 99.1)	35/38 (92.1, 77.5 to 97.9)	30/38 (78.9, 62.2 to 89.9)	1.00	0.11
Specificity	2701/3030 (89.1, 88.0 to 90.2)	2728/3030 (90.0, 88.9 to 91.1)	2915/3030 (96.2, 95.4 to 96.8)	0.001	<0.001
Positive predictive value	36/365 (9.9, 7.1 to 13.5)	35/337 (10.4, 7.4 to 14.3)	30/145 (20.7, 14.6 to 28.4)	0.82	0.001
Negative predictive value	2701/2703 (99.9, 99.7 to 100.0)	2728/2731 (99.9, 99.7 to 100.0)	2915/2923 (99.7, 99.4 to 99.9)	1.00	0.14
Screening efficiency‡	365/36 (10.1)	337/35 (9.6)	145/30 (4.8)	0.82	0.001
CIN3+					
Sensitivity	13/14 (92.9, 64.2 to 99.6)	12/14 (85.7, 56.2 to 97.5)	12/14 (85.7, 56.2 to 97.5)	1.00	1.00
Specificity	2702/3054 (88.5, 87.3 to 89.6)	2729/3054 (89.4, 88.2 to 90.4)	2921/3054 (95.6, 94.9 to 96.3)	0.001	<0.001
Positive predictive value	13/365 (3.6, 2.0 to 6.2)	12/337 (3.6, 1.9 to 6.3)	12/145 (8.3, 4.5 to 14.3)	1.00	0.03
Negative predictive value	2702/2703 (100.0, 99.8 to100.0)	2729/2731 (99.9, 99.7 to 100.0)	2921/2923 (99.9, 99.7 to 100.0)	1.00	1.00
Screening efficiency‡	365/13 (28.1)	337/12 (28.1)	145/12 (12.1)	1.00	0.03

≥ASC-US=atypical squamous cells of undetermined significance or higher grade; CI=confidence interval; CIN2+=cervical intraepithelial neoplasia grade 2 or worse; CIN3+=cervical intraepithelial neoplasia grade 3 or worse; HPV=human papillomavirus.
The 95% CIs for proportions were computed using the Wilson method.
*Differences in diagnostic accuracy between minipad HPV testing and clinician HPV testing were assessed using a McNemar test for paired proportions (sensitivity and specificity) or a x^2 test for proportions (predictive values and screening efficiency).
†Differences in diagnostic accuracy between minipad HPV testing and cytology were assessed using a McNemar test for paired proportions (sensitivity and specificity) or a x^2 test for proportions (predictive values and screening efficiency).
‡Screening efficiency: number of colposcopies required to diagnose CIN in one woman.

Among the 2703 participants with minipad based HPV negative results, complete genotype concordance was observed in 2683 (99.3%) and genotype discordance in 20 (0.7%). Supplementary appendix table S5 details the HPV genotype profiles of the 20 women.

Discussion

The results of this study suggest that minipad collected menstrual blood for HPV testing is an equivalent alternative or replacement to the current standard of care for cervical cancer screening, with non-inferior sensitivity and specificity for the detection of CIN2+ compared with clinician collected samples for HPV testing. Combined with standardised minipad based collection and the Early Test mobile app, HPV testing of minipad collected menstrual blood could resolve real world applicability and offer a practical pathway to expand access to screening.

Strengths and limitations of this study

Testing for HPV is currently a key component of cervical cancer screening, identifying high risk patients and enabling early interventions.[61 62] Clinician collected samples for HPV testing, although more sensitive than cytology testing, involve barriers as a result of sociocultural issues such as concerns about privacy and stigma[63 64]; healthcare costs, including travelling distances and waiting times at hospitals[65]; unequal distribution of medical resources, especially in remote and low resource areas[66]; and low health awareness and education.[67] Self-sampling methods, which enhance privacy and comfort, offer numerous advantages, serving as an alternative for individuals facing cultural or psychological obstacles,[68] providing a more convenient option for women with limited access to healthcare,[69] and reducing the demands for specialised medical resources and lowering the financial burden of screening.[70]

Compared with traditional invasive self-sampling,[9-11] using menstrual blood is preferred as an innovative, non-invasive self-sampling method.[21] The age range of menstruating women aligns well with the recommended age for cervical cancer screening.[37] Using menstrual blood for HPV testing is convenient, allowing women to non-invasively collect samples at home.[21] Self-collection not only respects women's privacy but also reduces their discomfort and alleviates fear of pain.[21 24] Nevertheless, in traditional Chinese culture, menstruation may be treated as a private matter, with menstrual blood considered as "polluting."[71] Our experience suggests that while cultural sensitivity in China and other Asian countries is important, education about HPV testing and the practical advantages of testing menstrual blood (convenience, privacy, and non-invasiveness) can transcend cultural barriers when properly implemented—for example, integrated with familiar digital platforms (WeChat) and government health initiatives. Consistently, several studies showed the strong preference of participants towards using menstrual blood for HPV testing in low resource settings in India.[27 30]

To standardise collection and eliminate variations from different sanitary pad brands, we developed the minipad sampling device, tailored for women with diverse sanitary pad usage. Similarly, a 2022 study used the Q-Pad to acquire menstrual blood specimens.[21] Although that study showed consistency for HPV testing with clinician sampling in a smaller cohort, our larger scale evaluation showed that minipad collected menstrual blood not only achieved high HPV concordance with clinician collected sampling (97.7%), but also demonstrated robust clinical performance in detecting cervical lesions. Minipad based HPV testing showed non-inferior specificity for detection of CIN2+ and equivalent colposcopy referrals (10.1 *v* 9.6 per participant with CIN2+) compared with traditional sampling.

Table 3 | Genotype concordance analysis between minipad HPV testing and clinician HPV testing. Values are number (percentage) unless stated otherwise

	Clinician sample test result			Type of concordance			
	HPV positive	HPV negative	κ (95% CI)	Complete	Partial*	Overall†	Discordance‡
Minipad test result:							
HPV positive (n=365)	317	48	0.891 (0.866 to 0.916)	268 (73.4)	45 (12.3)	313 (85.8)	52 (14.2)§
HPV negative (n=2703)	20	2683		2683 (99.3)	0 (0.0)	2683 (99.3)	20 (0.7)
Total (n=3068)	337	2731		2951 (96.2)	45 (1.5)	2996 (97.7)	72 (2.3)§

CI=confidence interval; HPV=human papillomavirus.
Screening positive: minipad collected HPV positive: detection of ≥1 of the 14 HPV genotypes (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) using minipad collected menstrual blood samples. Clinician collected HPV positive: detection of ≥1 of the 14 HPV genotypes (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) using clinician collected samples.
Screening negative: Minipad collected HPV negative: no detection of the 14 HPV genotypes (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) using minipad collected menstrual blood samples. Clinician collected HPV negative: no detection of the 14 HPV genotypes (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) using clinician collected samples.
*≥1 overlapping genotype with additional non-overlapping genotypes.
†Any overlap in HPV genotypes (complete+partial concordance).
‡No overlap in genotypes.
§In four samples, although both methods detected HPV positivity, the identified HPV types differed; thus these four diagnoses were classified as discordance.

In addition, the high sensitivity (94.7%) of minipad based HPV testing may confer a few benefits in cervical cancer screening populations. A positive HPV test result, although without CIN2+, may motivate women to seek out education about HPV and adopt preventive behaviours (eg, reduced sexual partners, condom use). This psychological alert effect can transform screening from passive surveillance to active health management. The high negative predictive value (99.9%) and exceptionally low false negative rate ensure minimal missed preventable cancers, which is a critical feature for a primary screening tool. Moreover, the integration with our Early Test mobile app further streamlined the reporting of results and patient communication, enhancing the feasibility of implementing large scale screening.

However, limitations of our study warrant careful consideration. Firstly, as menstrual blood flows through the genital tract, HPV can infect sites beyond the reach of conventional sampling methods, including the endocervical canal, vagina, and vulvar areas.[72-75] This broader anatomical sampling may identify more women with CIN that conventional samplings miss but also may create false positive results. Additional studies assessing triage markers to increase the specificity of HPV testing using menstrual blood are warranted. Secondly, women with dual negative results were treated as being negative for disease owing to the extremely low baseline prevalence of cervical lesions in this group (eg, Shanxi Province Cervical Cancer Screening study 0.07% (1/1511) CIN2+[39]; Swiss study 0/502[40]). This approach is common in large screening studies[9 51-53] and reflects routine clinical practice. We acknowledge that this might introduce verification bias, although given the extremely low expected prevalence among women with dual negative results, any bias is likely to be small (supplementary appendix table S6 and supplementary note 2). Thirdly, our diagnostic accuracy estimates were still limited by the screening sample size, warranting future studies of women with higher grade diagnoses.

Unanswered questions and future research

Through indirect comparison with clinician HPV testing, our findings show that minipad based HPV testing performs comparably to these established self-sampling strategies (supplementary appendix table S1 and supplementary note 3). However, direct comparative studies are needed to evaluate HPV testing of menstrual blood against established self-sampling methods (eg, vaginal swabs, cervicovaginal brushes), assessing not only diagnostic accuracy but also accessibility, particularly in under-served populations. Secondly, large scale implementation research must quantify gains from real world screening coverage, with longitudinal studies tracking recruitment, retention, and linkage-to-care rates. Real world trials should measure cost effectiveness and operational barriers in national programmes (supplementary appendix supplementary note 4).[76] Thirdly, future work should validate triage biomarkers for HPV testing of menstrual blood to optimise specificity and sensitivity, reducing unnecessary referrals to colposcopy.

Policy implications and conclusions

The findings of this study suggest that HPV testing of menstrual blood could be a robust alternative or replacement to clinician based testing, offering equivalent detection of high grade cervical lesions with screening efficiencies suitable for implementation at population level. Compared with clinician collected sampling and invasive self-sampling, non-invasive menstrual blood sampling enhances acceptability and feasibility for large scale screening. Integration with the standardised minipad and the Early Test digital platform optimises the processing of specimens, dissemination of results, and coordination of follow-up. These findings support the integration of menstrual blood based HPV testing into national cervical cancer screening guidelines.

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Data sharing: Deidentified data, statistical analysis codes, and study protocols are available as supplementary materials. The dataset (supplementary table S2) includes non-identifying ID, HPV results, cytology findings, and histological diagnosis. The annotated SPSS syntax files (supplementary files S4-S8) contain all the analytical codes. Supplementary file S2 provides detailed protocols for menstrual blood collection, laboratory processing, and data interpretation.

Transparency: The corresponding author affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

Dissemination to participants and related patient and public communities: We are committed to maximising the impact of this research. Study findings will be presented at major international conferences and shared with health authorities to support evidence based policy development. Clinical summaries will be distributed through professional medical societies and integrated into medical education programmes. To promote public engagement, plain language summaries will be developed for dissemination through social media platforms and collaboration with patient advocacy organisations. Additionally, companion blog posts targeting general audiences will be prepared to enhance accessibility. Press releases will be issued through medical media, and study investigators will be available for interviews to discuss the clinical implications and potential implementation of findings, particularly in underserved populations.

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Supplementary information: Supplementary appendix tables S1-S6, figure S1, supplementary notes 1-4, and supplementary files S1-S8